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Original Research Article

Assessment of Hypocalcemia in Neonates with Unconjugated Hyperbilirubinemia and its Association with Duration of Phototherapy

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Abstract

Aim: The aim of the present study wads to assess the prevalence of hypocalcemia in neonates with unconjugated hyperbilirubinemia receiving phototherapy and to observe association of hypocalcemia with duration of phototherapy.

Material & Methods: A prospective observational study conducted over a period of Jan 2019 to December 2019 among 200 neonates (both term and preterm) in the Department of Paediatrics, Government Medical College Bettiah, West Champaran, Bihar, India.

Results: The mean age of preterm and term neonates was 118.12±42.78 and 122.28±41.19. There were more males as compared to females in preterm and term neonates. Mean birth weight of preterm and term in this study were 2723.17±246.44 grams and 3132.78±370.90 grams respectively. 10 term neonates experienced hypocalcemia at 12 hours after starting of phototherapy. Similarly, 20 term neonates had hypocalcemia 48 hours after starting of phototherapy. None of the preterm neonates enrolled in the study experienced hypocalcemia after starting of phototherapy. It was observed that occurrence of hypocalcemia was not significantly associated with the duration of phototherapy. On comparing the 0 hours calcium level with subsequent hours, the mean difference in total serum calcium levels in both term, and preterm babies were found to be statistically significant and the difference was seen to be more significant in term babies. Correlation analysis of a duration of phototherapy with hypocalcemia showed a negative but insignificant correlation with a coefficient (r of −0.045 and a p=0.95).

Conclusion: A reduction in the serum calcium with increased duration of phototherapy, however, it does not fall to the level where treatment is required. Hence it is not recommended to monitor serum calcium levels in neonates receiving phototherapy.

Keywords: Hypocalcemia, Jaundice, Neonates Phototherapy

Introduction

Hyperbilirubinemia is a common and in most cases benign clinical condition in neonates. Phototherapy is used for management of neonatal hyperbilirubinemia. [1] Phototherapy may lead to complications including skin rash, diarrhea, hyperthermia, chills, dehydration, DNA damage to lymphocytes, retinal degeneration, bronze baby syndrome especially in cholestatic jaundice and PDA opening in LBWs and Hypocalcemia. [2] Romagnoli [3] was the first to suggest the association of hypocalcaemia and phototherapy in preterms. Hakinson [4] and Hunter[5] hypothesized that phototherapy inhibits pineal secretion of melatonin which blocks the effect of cortisol on bone calcium. [5] So cortisol increases bone uptake of calcium and induces hypocalcaemia. Kim [6] suggested decreased secretion of parathormone as the cause of hypocalcemia. In Hooman's study the urinary calcium excretion was significantly higher in phototherapy group. [7]

Complications of phototherapy are dehydration, diarrhea, skin rash, hyperthermia, retinal degeneration, DNA damage to lymphocytes, patent ductus arteriosus (PDA), bronze baby syndrome, and hypocalcemia. [2] Melatonin concentration is reduced in newborns with phototherapy which in turn leads to hypocalcemia. [8] First of all the association between phototherapy and hypocalcemia was reported by Shafiq MB et al. in

preterm infants. Phototherapy may lead to complications including skin rash, diarrhea, hyperthermia, chills, dehydration, DNA damage to lymphocytes, retinal degeneration, bronze baby syndrome especially in cholestatic jaundice and PDA opening in LBWs and Hypocalcemia. [10]

Besides the useful effects of phototherapy, some complications like hypocalcemia can be seen during the treatment with phototherapy. [10] It leads to inhibition of pineal gland by transcranial illumination, resulting in a decline in melatonin level and as a result, hypocalcemia develops. [11] Hypocalcemia refers to total serum calcium level less than 8 mg/dl in term neonates and less than 7 mg/dl in preterm neonates. [12] Hypocalcemia may cause cardiac and neurological dysfunctions. It may be symptomatic in the form of jitteriness, apnea, lethargy, stridor, irritability, and seizures. [13]

Hence, this study was undertaken to see occurrence of hypocalcemia in preterm and term neonates with hyperbilirubinemia receiving phototherapy, as phototherapy induced hypocalcemia can be a significant problem.

Material & Methods

A prospective observational study conducted over a period of Jan 2019 to December 2019 among 200 neonates (both term and preterm) in the Department of Paediatrics, Government Medical College Bettiah, West Champaran, Bihar, India.

Inclusion Criteria

All preterm (34 to less than 37 weeks) and term (37 to 40 weeks) neonates with jaundice and receiving phototherapy were included in the study.

Exclusion Criteria

Neonates with jaundice requiring exchange transfusion, birth asphyxia, sepsis, respiratory distress, ABO and Rh incompatibility, neonatal seizure, IUGR (Intrauterine growth retardation) babies, infants of diabetic mother and neonates with conjugated hyperbilirubinemia and prolonged jaundice were excluded from the study.

Methodology

The socio-demographic and clinical details of the neonates were recorded and entered in pre-designed proforma. In the enrolled neonates, serum total bilirubin and serum calcium levels at 0 hours, 12 hour and after 48 hours were sent in all cases. The serum calcium level estimated just before starting of phototherapy was considered as control and serum calcium level less than 7 mg/dl in preterm neonates and less than 8 mg/dl in term neonates is considered as hypocalcemia.

Statistical Analysis

Data were analyzed using statistical package for social sciences version 21 (SPSS). Continuous variables were described as mean and standard deviation and categorical variables in number and percentage. Hypocalcemia in term and preterm was compared using Fischer exact test. Pearson correlation was applied to see an association between hypocalcemia and the duration of phototherapy. Paired sample t-test was used to compare the means of calcium level before (0 hours) and after (12 hours, 48 hours) phototherapy; with a 95% confidence limit and $p<0.05$ was considered statistically significant.

Results

Table 1: Demographic profile of neonates admitted for neonatal hyperbilirubinemia

Variables		Preterm	Term
Age in hours (Mean ± SD)		118.12±42.78	122.28±41.19
Sex	Male	30	66
	Female	30	74
Gestational age in weeks (Mean ± SD)		36.24±0.76	37.83±0.84
Birth weight in grams (Mean ± SD)		2723.17±246.44	3132.78±370.90
TSB in mg/dl at 0 hours (Mean ± SD)		17.3±2.38	19.03±1.94
Serum calcium in mg/dl at 0 hours (Mean ± SD)		9.43±0.91	9.63±0.81
Duration of phototherapy in hours (Mean ± SD)		66±8.52	65.55±8.72

The mean age of preterm and term neonates was 118.12±42.78 and 122.28±41.19. There were more males as compared to females in preterm and term neonates. Mean birth weight of preterm and term in this study were 2723.17±246.44 grams and 3132.78±370.90 grams respectively.

Table 2: Serum calcium level at 12 hours and, after 48 hours

Duration of phototherapy	Serum calcium level	Preterm, n (%)	Term, n (%)	P value
At 12 hours	Hypocalcemia present	0	10	
	Hypocalcemia absent	60	130	1
	Total	60	140	
After 48 hours	Hypocalcemia present	0	20	
	Hypocalcemia absent	60	120	0.17
	Total	60	140	

10 term neonates experienced hypocalcemia at 12 hours after starting of phototherapy. Similarly, 20 term neonates had hypocalcemia 48 hours after starting of phototherapy. None of the preterm neonates enrolled in the study experienced hypocalcemia after starting of phototherapy. It was observed that occurrence of hypocalcemia was not significantly associated with the duration of phototherapy.

Table 3: Comparison of serum calcium at 0 hour with subsequent hours (at 12 hours and after 48 hours) in term and preterm neonates receiving phototherapy

Gestationalage (Weeks)	Comparison of serum calcium(Hours)	Mean paireddifference (mg/dl) ± SD	P value
Preterm(34-37)	0 and at 12	0.518±0.602	0.006
	0 and after 48	0.713±0.858	0.007
Term (38-41)	0 and at 12	0.528±0.712	<0.001
	0 and after 48	0.915±0.775	<0.001

On comparing the 0 hours calcium level with subsequent hours, the mean difference in total serum calcium levels in both term, and preterm babies were found to be statistically significant and the difference was seen to be more significant in term babies.

Table 4: Correlation of hypocalcemia in term neonates with duration of phototherapy

Correlation	R	CI for r	P value
Negative	-0.045	-0.740 to 0.773	0.95

Correlation analysis of a duration of phototherapy with hypocalcemia showed a negative but insignificant correlation with a coefficient (r of −0.045 and a p=0.95).

Discussion

Jaundice is the yellowish coloration of the skin, sclera, and mucus membrane resulting from the accumulation of bilirubin. [14] It is a common morbidity observed in the neonate during the first week of life in approximately 60% of term and 80% of preterm neonates.2 In most of the neonates no intervention is required however, 5-10% of the cases have clinically significant jaundice, which requires treatment. [15,16] High level of unconjugated bilirubin may cause permanent neurological damage. [17,18] There are various modalities of treatment for neonatal hyperbilirubinemia and, phototherapy is one of them. Besides the useful effects of phototherapy, some complications like hypocalcemia can be seen during the treatment with phototherapy. [19] Hypocalcemia is a significant problem in neonates subjected to phototherapy and its prevalence in full term neonates is 8.7%.20 Hypocalcemia developed in 39% of term and 53% of preterms after being subjected to phototherapy for more than 48 hours. [21] Hypocalcemia, being a major complication of phototherapy, is associated with poor prognosis in terms of high mortality rate as compared to babies with normocalcemia, if not diagnosed timely and treated accordingly. [21,22]

The mean age of preterm and term neonates was 118.12±42.78 and 122.28±41.19. There were more males as compared to females in preterm and term neonates. Mean birth weight of preterm and term in this study were 2723.17±246.44 grams and 3132.78±370.90 grams respectively. In a study done by Taheri et al mean birth weight in term neonates was 3182±430 grams which were agreed with the term neonates of our study. [23] Hypocalcemia refers to total serum calcium level less than 8 mg/dl in term neonates and less than 7 mg/dl in preterm neonates. [24] Hypocalcemia may cause cardiac and neurological dysfunctions. It may be symptomatic in the form of jitteriness, apnea, lethargy, stridor, irritability, and seizures. [25]

10 term neonates experienced hypocalcemia at 12 hours after starting of phototherapy. Similarly, 20 term neonates had hypocalcemia 48 hours after starting of phototherapy. None of the preterm neonates enrolled in the study experienced hypocalcemia after starting of phototherapy. It was observed that occurrence of hypocalcemia was not significantly associated with the duration of phototherapy. In the study by Chandrashekhar[26] prevalence of hypocalcemia was seen in 11%, 27%, and 68.5% at 24 hours, 36 hours, and 48 hours of phototherapy in preterm neonates and 6%, 14%, and 16% at 24 hours, 36 hours and 48 hours of phototherapy in term neonates respectively however, in this study serum calcium level of less than 7 mg/dl was considered as hypocalcemia in both term and preterm which is in contrast to this study. Phototherapy is the most effective therapy for management of neonatal hyperbilirubinemia which lowers serum bilirubin level by converting bilirubin into non-toxic excretable form. [27] Phototherapy converts unconjugated bilirubin to more polar stereoisomer by a process called photo isomerization. The substance formed cannot cross the blood brain barrier and is not neurotoxic and later on excreted out of the body via urine and bile. [28]

On comparing the 0 hours calcium level with subsequent hours, the mean difference in total serum calcium levels in both term, and preterm babies were found to be statistically significant and the difference was seen to be more significant in term babies. Correlation analysis of a duration of phototherapy with hypocalcemia showed a negative but insignificant correlation with a coefficient (r of −0.045 and a p=0.95). This indicates that the duration of phototherapy causes little or no significant hypocalcemia in term neonates before the discharge. However, no similar studies have been published to date which could indicate or determine the correlation between the duration of phototherapy and hypocalcemia before discharge i.e., after 48 hours.

Conclusion

The present study concluded that though there is a reduction in the serum level of calcium with increasing duration of phototherapy, it does not fall to the level where treatment is required. Hence it is not recommended to monitor serum calcium levels in neonates receiving phototherapy.

References

1. Fanaroff A, Wlash M. Neonatal–Perinatal Medicine, Diseases of the Fetus and Infant, 9th edn, Elsevier Mosby, 2010; Pp: 1443-1481.
2. Xiong T, Qu Y, Cambrier S, Mu D. The side effects of phototherapy for neonatal jaundice; What we do? What should we do? Eur J Pediatr 2011;170(10):1247-55.
3. Romagnoli C, Polidori G, Cataldi L, Tortorolo G, Segni G. Phototherapy-induced hypocal cemia. The Journal of pediatrics. 1979 May 1; 94(5):815-6.
4. Hakanson D, Penny R, Bergstrom WH. Calcemic responses to photic and pharmacologic manipulation of serum melatonin. Pediatr Res 1987; 22(4):414-6.
5. Hunter KM. Hypocalcemia. In: Cloherty JP, Eichenwald CE, Stark AR(eds). Manual of Neonatal Care 5th ed. Philadelphia: Lippincott wiliams& Wilkins. 2004; Pp: 579-88.
6. Kim SH, Park JH. Effect of phototherapy on bone metabolism in newborn rats. J Korean Soc Neonatal 2001;8(2):206-10.
7. Hooman N, Honarpisheh A. The effect of phototherapy on urinary calcium excretion in newborns. Pediatr Nephrol 2005; 20(9):1363-4.
8. Kargar M, Jamshidi Z, Beheshtipour N, Pishva N, Jamali M. Effect of Head Covering on Phototherapy-Induced Hypocalcemia in Icterus Newborns; A Randomized Controlled Trial. IJCBNM 2014;2(2):121-6.
9. Shafiq M, Ahmed Z, Ahmad A. Validity of visual assessment of neonatal jaundice for screening significant hyperbilirubinemia. PAFMJ 2019;69(1),212-16.
10. Bhat JA, Sheikh SA, Wani ZA, Ara R. Prevalence of hypocalcemia, its correlation with duration of phototherapy and persistence in healthy term newborns after intensive phototherapy: A prospective observational hospital-based observational study. Imam J Appl Sc. 2019;4(2):57- 61.
11. Karamifar H, Pishva N, Amirhakimi GH. Prevalence of phototherapy induced hypocalcemia. IJMS 2002; 4:166–168.
12. Tsang RC, Koo WK. Calcium and Magnesium Homeostasis. In: MacDonald MG, Seshia MK, editors. Avery's Neonatology: Pathophy siology and Management of the Newborn. 7th ed. New Delhi: Wolters Kluwer Pvt Ltd. 20 16;653.
13. Arora S, Narang GS, Singh G. Serum calcium levels in preterm and term neonates on phototherapy. J of Nepal Paediatr Soc. 2014; 34(1):24-8.
14. Rennie J, Burman-Roy S, Murphy MS. Neonatal Jaundice: summary of NICE guidance. BMJ. 2010;340:2409.
15. Bahbah MH, ElNemr FM, ElZayat RS, Aziz EA. Effect of phototherapy on serum calcium level in neonatal jaundice. Menoufia Med J. 20 15;28(2):426-30.
16. Jagannath HN. Association between phototherapy and serum calcium levels in newborns: A institutional cross-sectional study. Int J Paediatrics Geriatrics. 2020;3(1): 151-4.
17. Otero Regino W, Velasco H, Sandoval H. The protective role of bilirubin in human beings. Revista colombiana de Gastroenterología. 2009;24(3):293-301.
18. Kale AV, Jadhao PU, Valecha A, Kethepalli S. The effect of phototherapy on serum calcium level in neonates with hyperbilirubinemia: a cross sectional study. Int J Contemp Pediatr. 2020;7(8):1772-6.
19. Bhat JA, Sheikh SA, Wani ZA, Ara R. Prevalence of hypocalcemia, its correlation with duration of phototherapy and persistence in healthy term newborns after intensive phototherapy: A prospective observational hospital-based observational study. Imam J Appl Sc. 2019;4(2):57-61.
20. Arora S, Narang GS, Singh G. Serum Calcium Levels in Preterm and Term Neonates on Phototherapy. J Nepal Paediatr Soc 2014;34 (1):24-8.
21. Jain SK. Evaluation of effect of phototherapy on serum calcium level. Medpulse-International Med J 2015;2(6):316-8.
22. Bhutani VK, Zipursky A, Blencowe H, Khanna R, Sgro M, Ebbesen F. Neonatal hyperbilirubinemia and Rhesus disease of the newborn: incidence and impairment estimates for 2010 at regional and global levels. Pediatr Res, 2013;1:86–100.

23. Taheri PA, Sajjadian N, Eivazzadeh B. Prevalence of phototherapy induced hypocalcemia in term neonate. Iran J Pediatr. 2013;23(6):710-1.
24. Tsang RC, Koo WK. Calcium and Magnesium Homeostasis. In: MacDonald MG, Seshia MK, editors. Avery's Neonatology: Pathophy siology and Management of the Newborn. 7th ed. New Delhi: Wolters Kluwer Pvt Ltd. 201 6;653.
25. Arora S, Narang GS, Singh G. Serum calcium levels in preterm and term neonates on phototherapy. J of Nepal Paediatr Soc. 201 4;34(1):24-8.
26. Chandrashekar B, Venugopal S, Veeresh SM. Effect of duration of phototherapy on serum calcium level in newborn with neonatal jaundice. Pediatr Rev Int J Pediatr Res. 2014; 1:88-92.
27. Sachdeva M, Murki S, Oleti TP Kandraju H. Intermittent versus continuous phototherapy for the treatment of neonatal non-hemolytic moderate hyperbilirubinemia in infants more than 34 weeks of gestational age: a randomized controlled trial. Eur J Pediatr 2015;174(2):177-81.
28. Siyal AR, Khoja Rabia NA, Hemandas. Determinations of clinical presentations and risk factors of neonatal hyperbilirubinemia. Ann. Pak. Inst. Med. Sci. 2017;13(1):35-38.